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Young Investigator Awards Competition

HYPERGLYCEMIA OF ADULT ZEBRAFISH LEADS TO CARDIAC REMODELING AND DYSFUNCTION VIA NKX2.5-CALRETICULIN-P53 SIGNALING PATHWAY

Oral Contributions
Room 10
Sunday, March 15, 2015, 8:15 a.m.-8:30 a.m.

Session Title: Young Investigator Awards Competition: ACC Herman K. Gold Young Investigator Awards in Molecular and Cellular Cardiology
Abstract Category: Molecular and Cellular Cardiology
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Background: The prevalence of diabetes mellitus is continuing to increase at an alarming rate, and cardiovascular complications have been the major cause of mortality in diabetic patients. However, these pathogenetic mechanisms have not been thoroughly elucidated. Adult zebrafish has shown the potential to study various cardiovascular diseases; it is of great necessity to make further study on hyperglycemia-induced changes in myocardium via zebrafish model in vivo and vitro.

Methods and Results: Hyperglycemia was induced in zebrafish by immersing them in glucose solution. Transmission electron microscopy (TEM) showed significantly increased mitochondrial number and area, and mitochondrial cavity changes. Hearts of the treated group become larger than the wild-type, gradually exhibiting characteristics such as lessened myocardium in H&E staining, strong myocardial fibers and obvious myocardial apoptosis in immunostaining. Electrocardiographic analysis revealed reduced heart rate, increased incidence of ST-T change and voltage alternation in the treated group. Echocardiographic studies demonstrated impaired ejection fraction (EF) and cardiac output (CO), accompanied by enlarged ventricular dimensions. Real-time PCR indicated the activation of fetal genes (nppa and nppb, known markers of cardiac hypertrophy and heart failure) and increased expressions of NKX2.5 and its downstream genes calreticulin (CRT) and p53 in the treated group. When cultured primary cardiomyocytes were exposed to glucose or shz-1, a specific activator of NKX2.5, the incremental mRNA and protein expressions of NKX2.5, CRT and p53 were observed respectively.

Conclusion: Both cardiomyocyte hypertrophy and apoptosis are involved in the cardiac remodeling process of zebrafish with hyperglycemia. Lessened myocardium and decompensated cardiac function make apoptosis even more critical. The NKX2.5-Calreticulin-p53 signaling pathway plays a vital role in myocardial apoptosis, resulting in cardiac dysfunction eventually. Further research should be performed more on molecular pathways to obtain a better understanding of pathogenesis and new targets for intervention.